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U.S. APPLICATION NO.
To be assigned 09/308607

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP97/04288	**25.November.1997**	**25.November.1996**

TITLE OF INVENTION
PROCESS FOR PRODUCING CERAMICS

APPLICANT(S) FOR DO/EO/US
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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/LUS).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items below concern other document(s) or other information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Small entity claim with a copy of this transmittal letter attached.
17. ☒ International search report.
18. ☐ International preliminary examination report.
19. ☒ Extra set of drawings
20. ☐
21. ☐

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U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NO.
To Be Assigned	**PCT/JP97/04288**	**34650/DBP**

☒ The following fees are submitted: (see Note (1) below)	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-5)):		
Search Report has been prepared by the EPO or JPO ..... **$ 840.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... **$ 670.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... **$ 760.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... **$ 970.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... **$ 96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$ 840.00**	
Surcharge of **$130** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	**10**[+4] -20=	**0**	**X $18**	**$ 0.00**	
Independent Claims	**4** -3=	**1**	**X $78**	**$ 78.00**	
Multiple dependent claim(s) (if applicable)			**+ $260**	**$ 260.00**	
			TOTAL OF ABOVE CALCULATIONS =	**$ 1,178.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
			SUBTOTAL =	**$ 1,178.00**	
Processing fee of **$130** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
			TOTAL NATIONAL FEE =	**$ 1,178.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property				**$ 40.00**	
			TOTAL FEES ENCLOSED =	**$ 1,218.00**	
Note (1): The basic national fee must be paid when filing this application. The 20-month time limit (37 CFR § 1.494) and 30-month time limit (37 CFR § 1.495) are not extendable.				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$ 1,178.00 (filing fee) and $40.00 (recording fee)** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **03-1728**. A duplicate copy of this sheet is enclosed.

NOTE (2): Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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34650/DBP/A400
English Translation of International Application

DESCRIPTION

PROCESS FOR PRODUCING CERAMICS

TECHNICAL FIELD

The present invention relates to a process for producing ceramics, more specifically relates to a process for producing porous ceramics suitable for use as a bone filler or a DDS carrier. The present invention further relates to composite spherical-shape ceramics suitable for use as a medical or dental bone filler or bone cement or other bioceramic material or various resorbable carriers etc.

BACKGROUND ART

In the past, as ceramics having superior biocompatibility, in the field of bone fillers and bone cement, calcium phosphate has been broadly used. The forms at the time of use have mostly been splinter-powder (break to powder), blocks, porous substances, self-setting cements, etc. In particular, in bone fillers, some splinter-powder (break to powder) and blocks have been commercialized.

As an example of application of calcium phosphate, recently attention has been made to the use for DDS carriers. For example, Japanese Unexamined Patent Publication (Kokai) No. 60-106459 discloses a process for producing a sustained drug release type carrier comprising coating combustible beads with calcium phosphate and then sintering them to cause the combustible beads to burn away and leave hollow beads of calcium phosphate, then filling a drug into the hollow portions. Further, Japanese Unexamined Patent Publication (Kokai) No. 59-101145 discloses a process for producing a carrier having a similar effect by impregnating a drug into porous calcium phosphate having open pores.

However, in the above processes, the production steps, such as the injection of the drug into the hollow beads, becomes complicated. Further, it is difficult to

control the rate of sustained release of the drug. In the latter process as well, similarly there is a concern over problems such as the complexity of the production steps and the difficulty of control of the rate of sustained release.

On the other hand, spherical-shape calcium phosphate is used as a column filler for liquid chromatography. The general production process is a spray drying granulation method. The spray drying granulation method is generally used for the production of particles having a particle size of 100 μm or less. An extremely large-sized apparatus is required when producing larger particles. Further, as a process for producing spherical-shape calcium phosphate having a size of 100 μm or more, Japanese Unexamined Patent Publication (Kokai) No. 64-75030 discloses a process comprising injecting a ceramics slurry into an oil phase to form a water-in-oil emulsion, then injecting this again into a water phase to solidify the oil phase, followed by sintering to burn off the oil phase, whereby spherical-shape calcium phosphate is obtained.

However, for use as a bone filler, particles having a size of 100 μm or more are desirable. Capital investment is required for producing this by the spray drying granulation method, and therefore, the costs are increased. Further, in the process disclosed in Japanese Unexamined Patent Publication (Kokai) No. 64-75030, production steps for adjusting the oil phase etc. become necessary, and therefore, there are again concerns of increased cost.

An application for DDS requires a superior drug carrying property, biocompatibility, sustained drug release, and biodegrarative. Calcium phosphate is superior in biocompatibility and resorption in the living body or organism. In the past, considerable research went into its application for DDS, but nothing has been commercialized yet. One of the reasons is that, since it

is ceramics, it is hard to process. Porosity has to be imparted in order to carry a drug, but it is difficult to change conditions such as the size, strength, distribution of pores, etc. Further, from the viewpoint of the rate of filling in the diseased location or operability, it is desirable that DDS carriers and bone fillers be spherical. Since it is extremely difficult to process ceramics into spheres, this has not yet been commercialized.

Spherical-shape particles have applications in a broad range of fields such as processing powders and carrying catalysts, so that the spherical-shape particles which can be supplied to these fields, it is particularly preferable or sought to produce them in a manner enabling the particle size to be changed in depending upon the order and to enable the particles themselves to functionally carry various substances.

In the medical field, the properties of the particles themselves have come under focus along with the development of drug delivery systems which use particles to carry a drug and effectively release the drug at the desired location in the organism.

Further, in biomaterials as well, calcium phosphate is being broadly used in the fields of bone fillers and bone cement as ceramics superior in biocompatibility. The shapes at the time of use are mostly splinter-powder (break to power), blocks, porous substances, self-setting cement, etc. In particular, in bone fillers, some splinter-powder (break to powder) or blocks have been commercialized.

Japanese Unexamined Patent Publication (Kokai) Nos. 3-131580 and 1-314572 disclose processes of preparation of a porous block of calcium phosphate ceramics. In these processes, it is necessary to shape the block at the time of surgery to match the shape of the bone loss. Further, the implanted block member is often scattered or ejected from the organism before the fusion with the newly grown

bone.

To overcome this problem, that is, to cause the granules to fix with each other, Japanese Unexamined Patent Publication (Kokai) Nos. 60-256460 and 60-256461 attempt to use a fibrin paste as a glue. However, a fibrin paste is produced from human blood, therefore had the risk of infection by hepatitis, AIDS, etc.

Further, Japanese Unexamined Patent Publication (Kokai) No. 59-88351 and No. 59-182263 disclose processes for producing a bone repair cement having α-tricalcium phosphate or tetracalcium phosphate as its main ingredient. In these processes, the cement cures at the bone loss portion, then fixes to it densely, so osteoblasts and other tissue and cells will not enter the inside of the filler such as with a porous block. Therefore, the bone substitution ability of a calcium phosphate porous block is superior.

The conventional granular bone filler or porous calcium phosphate block often scatters before fusion with the newly grown bone when implanted in a bone loss portion. Further, the bone cement is inferior in bone substitution capability compared with a porous calcium phosphate bone filler due to the fact that it fixes densely after curing. Therefore, a granular bone filler or porous calcium phosphate block capable of achieving anchoring or preventing scattering at the bone loss portion is preferred. No bone filler having both the functions of a bone filler and bone cement has yet been commercialized.

DISCLOSURE OF THE INVENTION

Accordingly, an object of the present invention is to provide a technique for easily processing a hard-to-process calcium phosphate ceramics into a spherical shape, whereby an effective means of treatment of cancer or bone tumors by impregnation of a drug and administration to the diseased portion is provided, since the spherical-shape ceramics has pores and a resorption

in the organism optimal for DDS.

Another object of the present invention is to enable the simple and easy production of spherical-shape ceramics having a functional composite layer having a porous inside and having an outer periphery with different physical properties from the inside, more particularly, to provide a bone filler which enables fusion with newly grown bone or bone substitution action quickly in a natural manner, without scattering, when filled in a bone loss portion and a process of production of the same.

In accordance with the present invention, there is provided a process for producing ceramics by dropping starting ceramics into a low temperature medium, followed by freeze drying and, then sintering.

In accordance with the present invention, there is further provided composite spherical-shape ceramics having a composite layer obtained by dropping a starting material powder into a low temperature medium applying a hydrothermal treatment to the resultant spherical-shape ceramics.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will now be explained in detail with reference to the drawings.

Figures 1(a) and 1(b) are scanning-type electron micrographs of the surface of porous ceramics powder shown in Example I-2 (100X and 1000X, respectively).

Figures 2(a) and 2(b) are scanning-type electron micrographs of the sliced cross-section of porous ceramics powder shown in Example I-2 (100X and 1000X, respectively).

Figures 3(a), 3(b), 3(c), 3(d), 3(e), 3(f), 3(g), 3(h), 3(i), and 3(j) are scanning-type electron micrographs showing the mode of dissolution along with time of the porous ceramics shown in Example I-4 in ion exchange water.

Figures 4(a) and 4(b) are scanning-type electron

micrographs of the frozen sliced cross-section of porous ceramics shown in Example I-5 (1000X and 3000X, respectively).

Figure 5 is a graph of the results of Example I-6.

Figures 6(a) and 6(b) are scanning-type electron micrographs after immersion in a refrigerant in the production process of the spherical-shape ceramics of the present invention (150X and 1000X, respectively).

Figures 7(a) and 7(b) are scanning-type electron micrographs after the hydrothermal treatment in the process of production of the spherical-shape ceramics of the present invention (150X and 1000X, respectively).

Figures 8(a) and 8(b) are scanning-type electron micrographs after cement coating in the process of production of the spherical-shape ceramics of the present invention (150X and 1000X, respectively).

BEST MODE FOR CARRYING OUT THE INVENTION

A first embodiment of the present invention will now be explained.

Calcium phosphate synthesized by a known synthesis method, preferably wet synthesis or dry synthesis, preferably hydroxyapatite, tricalcium phosphate, calcium dihydrogenphosphate, tetracalcium phosphate, octacalcium phosphate, calcium phosphate glass, or mixtures thereof calcium phosphates, more preferably tricalcium phosphate, is made into a powder, preferably not more than 100 microns, using a pulverizer or spray dryer etc. Into this powder is added, stirred, and mixed a binder slurry, preferably, an aqueous solution of one or more of a water-soluble cellulose derivative, polyvinyl alcohol, polyacrylic acid, polyacrylamide, polyvinyl pyrrolidone, polyethylene glycol, and starch, more preferably a 3 to 15% by weight aqueous solution of polyvinyl alcohol or polyethylene glycol in an amount of 1 to 5 times, preferably 2 to 4 times, of the weight of the powder. At this time, a similar result can be obtained even if using a 10 to 50% by weight slurry of calcium phosphate other

than the powder.

As the ceramics in the present invention, in addition to the above-mentioned calcium phosphate ceramics, alumina, zirconia, carbon, etc. may be mentioned.

The above-mentioned binders are merely examples. In addition, additives may sometimes be added depending upon the mode of use etc., for example, a glycol may be added as a stabilizing agent. Further, if not a porous state, the binder may not be necessary.

The calcium phosphate slurry obtained containing a binder is filled into a cylinder and is dropped from a thin tube attached to the front end of the cylinder, preferably having an inner diameter of 0.3 to 2 mm, into a low temperature refrigerant solution prepared in advance and having a temperature of about -10°C or less, preferably, liquid nitrogen, liquid helium, acetone + dry ice, methanol + dry ice, or ethyl ether + dry ice.

The dropped calcium phosphate slurry containing the binder becomes spherical shape during its fall and at the surface of the liquid nitrogen and can be frozen, while maintaining the spherical shape.

The frozen slurry obtained is freeze-dried so as not to thaw and to completely remove the moisture. The spherical-shape calcium phosphate thus obtained is sintered using an electric furnace at 800°C to 1500°C, preferably 1000°C to 1400°C, to obtain the spherical-shape ceramics.

The diameter of the ceramics powder obtained by this production process is 0.01 to 10 mm, but can be adjusted in various ways by the mode of contact such as the dropping conditions.

In the present invention, it is sufficient to bring the ceramics solution into contact with a low temperature refrigerant. Various modes of contact are possible, but other than the dropping, spraying by an atomizer such as a spray dryer, pressurized spraying by a spray, contact

with a container in by injection, pouring, and other means of introduction into a container, etc. may be mentioned.

The spherical-shape ceramics has fine pores formed at the time of evaporation of the binder over the spheres as a whole. A drug etc. may be impregnated into the ceramics from these pores. Further, the diameter of the pores may be varied by the content of the binder. Further, since the pores can be plugged by a known calcium phosphate cement or other synthetic resin etc., control of the rate of sustained release is possible.

Due to the uniform porosity, the sustainability of the sustained release in the orgnism is, for example, units of several days or several weeks in the body fluids, more specifically for one week to three weeks. A similar sustainability can be obtained in the body tissue as well.

Therefore, by filling this spherical-shape ceramics into a portion of bone loss, since the pores, one of the features of this spherical-shape ceramics, do not block the flow of blood, it is possible to quickly regenerate the bone. Further, the effect can be enhanced further by impregnating the pores with bone-growth factors, collagen, antibiotics, and other drugs.

The present invention, in addition to the above, may be used as a main material or additive etc. for various products such as orally administered drugs, processed foods, beverages, various adsorption column materials, cosmetics, dentifrices, fumigants, air fresheners and deodorizing agents, bath additives, facial cleansers, shampoos, and other toiletries, fibers having adsorption or other functions or paper materials and other fields requiring adsorption and sustained release of the carried substances.

In this above way, a good sustained release drug can be obtained by carrying various drugs. Due to the superior sustained release, for example, penicillin type

antibiotics, tetracycline type antibiotics, the anticancer drugs 5FU, carboplatin, cisplatin, etc. are preferably used.

The specific production process of composite spherical-shape ceramics according to the second aspect of the present invention comprises mixing a binder into a high purity calcium phosphate powder obtained by a known synthetic method, preferably wet synthesis and dry synthesis, preferably a hydroxyapatite, tricalcium phosphate, or tetracalcium phosphate, then shape the mixture by any method and sinter it at a temperature of 800 to 1500°C to obtain a calcium phosphate ceramics superior in biocompatibility. As the method of shaping, a monoaxial press, rubber press, etc. may be used for easy shaping. Further, by mixing a burn-off substance in the binder, it is possible to make the ceramics porous after sintering. Porous ceramics facilitate the entry of osteoblasts and other tissue in the organism and a bone regenerating capability to be exhibited more suitably, when implanted in a bone loss portion. However, since the dynamic strength is poor, it is necessary to pay close attention at the time of use.

The porous or dense calcium phosphate ceramics obtained, and a suitable amount of ion exchange water are placed in a heat resistant sterile bottle and heated in a sealed atmosphere at 80°C to 150°C, preferably 100°C to 120°C, for at least 30 minutes, preferably 12 to 24 hours to cause high purity calcium phosphate crystal to precipitate on the surface of the ceramics (hereinafter this technique is called "hydrothermal treatment"). The crystal is comprised of the phosphoric acid and calcium eluted from the surface of the sintered product reprecipitating on the surface of the ceramics. Therefore, an extremely high purity calcium phosphate crystal precipitates over the entire surface of the ceramics. The particles of ceramics grow by the sintering and the specific surface area rapidly drops. However, by

using the above process to cause crystals to precipitate on the surface, the specific surface area can be restored to a certain extent again. By increasing the specific surface area, it is possible to obtain an anchoring effect in the organism even if used as a bone filler in this state.

The hydrothermal treatment in the present invention may be performed by causing crystal to precipitate in steam using an autoclave in addition to the above technique. More specifically, this consists of heating the mixture under a sealed steam atmosphere in an autoclave at 80°C to 150°C, preferably 100°C to 120°C, for at least 30 minutes, preferably 12 to 24 hours so as to cause high purity calcium phosphate crystal to precipitate on the surface of the ceramics. Further, in the process using a heat resistant sterilize bottle or the process using an autoclave, it is possible to reduce the hydrothermal treatment time and control the precipitated layer by using an aqueous solution for impregnated with the ceramics and an aqueous solution containing calcium, phosphate, or other ions in a steam atmosphere.

In this hydrothermal treatment, the width of the precipitated layer is controlled by the treatment time, amount of pressure, pressurizing temperature, treatment atmosphere, etc. Specifically, it may be suitably selected depending upon the application such as the bone filler, DDS carrier, dental root canal filler, ceramics adsorbent, column chromatography filler, or other application.

The coating method of a cement on the surface of a bone filler, without impairing, the setting (or curing) function, to enhance the anchoring effect is explained below. The calcium phosphate ceramics with crystal precipitated on the surface thereof is mixed with a bone cement which cures by kneading with water and a setting (or curing) solution. As the bone cement, α-tricalcium

phosphate, tetracalcium phosphate, octacalcium phosphate, calcium sulfate, or any mixture thereof is preferable as the cement.

Further, the present invention is not limited in biomaterials. Any fine particles having the composite layer, in particular porous fine particles, which can be made to carry various substances in the porous portions are particularly preferred.

After mixing, a suitable amount of ion exchange water is added and quickly kneaded. The cement is instantaneously frozen in liquid nitrogen, liquid helium, or another super-low temperature medium or super-low temperature atmosphere before the cement completely sets (or cures). A bone cement has a large specific surface area. The crystal growth starts by a hydrolysis reaction when moisture adheres to the cement surface. By mixing and kneading this with a cement material, the bone cement in the intervals of the crystals precipitated on the surface of the ceramics can stop the crystal growth due to the setting by the instantaneous freezing. The instantaneously frozen bone cement and bone filler are then freeze-dried. The freeze-drying can completely remove the moisture while maintaining the specific surface area of the cement to a certain extent. Therefore, it is possible to separate the dried product obtained into the bone filler and cement, then cause it to function as cement again.

Bone cement is taken into the intervals of the crystal reprecipitated on the surface of the bone filler. The bone cement taken in secures the specific surface area required for setting due to the freeze-drying. Therefore, the bone filler according to the present invention is a bone filler coated on the surface thereof with a setting type bone cement. When implanted in a bone loss portion, it can bond with the portion by the setting action of the surface and effectively prevent the bone filler from scattering after implantation. Further, by

making the core ceramics porous, there is the same bone substitution ability as a granular porous filler.

As explained above, as the drug carried, a broad range of drugs can be used. Further, since the surface is treated by reprecipitation, the rate of dissolution in the organism is adjusted, therefore the function becomes extremely marked.

A good sustained release drug is obtained by carrying various drugs. Due to the superior sustained release, for example, penicillin type antibiotics, tetracycline type antibiotics, the anticancer drugs 5FU, carboplatin, cisplatin, acrarubicin hydrochloride, daunorubicin hydrochloride, neocartinostatin, acutinomycin D, pepromycin sulfate, piralbicin hydrochloride, doxorubicin hydrochloride, bleomycin hydrochloride, bleomycin sulfate, mitomycin, and other drugs may be suitably used.

In the second embodiment of the present invention as well, in addition to the above, the present invention may be used as a main material or substrate etc. for various products such as orally administered drugs, processed foods, beverages, various adsorption column materials, cosmetics, dentifrices, fumigants, air fresheners and deodorizing agents, bath additives, facial cleansers, shampoos, and other toiletries, fibers having adsorption or other functions or paper materials and other fields requiring adsorption and sustained release of the carried substances.

Examples

The present invention will be explained in more detail with reference to Examples, but the present invention is of course not limited to these Examples in scope.

Example I-1

1 g of calcium phosphate powder (#400 mesh or less) having Ca/P = 1.48 synthesized by a known wet synthesis method was mixed into 3 g of a 10% by weight aqueous

solution of polyvinyl alcohol, then 0.5 g of ion exchange water was added and the mixture further mixed and stirred. 10 ml of the slurry obtained was filled into a thermosyringe and a 24G needle (inner diameter 0.47 mm) was used to drop it into liquid nitrogen. The frozen product obtained was dried using a vacuum freeze dryer, then was sintered at 1400°C for 5 hours to obtain 0.9 g of spherical-shape ceramics. The spherical-shape ceramics obtained had a diameter of 0.8 to 1.2 mm. Powder X-ray measurement confirmed that the spherical-shape ceramics was a single phase of α-tricalcium phosphate.

Example I-2

The spherical ceramics prepared in Example I-1 was observed by a scanning-type electron microscope (SEM). The sample was observed by two types of methods: the surface of the sample and the sliced section of the sample. As a result, the surface of the sample was observed to have pores of 1 to 4 μm distributed over its entire surface. Further, the SEM image of the sliced section showed that there were pores of 100 to 200 μm inside the spherical-shape ceramics. It was confirmed that there was a mozaic structure of calcium phosphate around it. (See Figs. 1(a) and 1(b) and Figs. 2(a) and 2(b).)

Example I-3

The spherical ceramics prepared in Example I-1 was immersed in red ink, then deaerated under vacuum for about 10 minutes. This was returned to ordinary pressure, then the excess ink was wiped off and the sample dried by freeze-drying in vacuum. The sample was sliced at its center portion, whereupon it was confirmed that the red ink had penetrated to the inside of the ceramics. Therefore, it is possible to easily impregnate a drug by just a short period of vacuum deaeration.

Example I-4

The spherical-shape porous ceramics prepared in Example I-1 was immersed in 50 ml of ion exchange water

for 1 hour, 1 day, 3 days, 7 days, and 14 days and the form of dissolution was observed over time by a scanning-type electron microscope. The obtained electron micrographs are shown in Fig. 3(a) (1 hour, 500X), 3(b) (1 hour, 1000X), 3(c) (1 day, 500X), 3(d) (1 day, 1000X), 3(e) (3 days, 500X), 3(f) (3 days, 1000X), 3(g) (7 days, 500X), 3(h) (7 days, 1000X), 3(i) (14 days, 500X), and 3(j) (14 days, 1000X). The sample was a spherical-shape porous ceramics for a drug carrier superior in resorption in the body.

As a result, it was confirmed that the spherical-shape porous ceramics quickly dissolved and the state of dissolution occurred with units of clump of grain peeling off in a plate shape. A similar trend may be seen in the body as well. This material was shown to be a material which is finally completely resorbed while releasing the drug.

Example I-5

The spherical-shape porous ceramics prepared in Example I-1 was immersed in a dispersion of fine hydroxyapatite particles and subjected to ultrasonic waves, while being vacuum deaerated. Then, the sample was frozen and sliced and observed under a scanning-type electron microscope.

As a result, fine hydroxyapatite particles were filled in the fine pores of spherical-shape porous ceramics. Hydroxyapatite has a superior absorbing action. It is possible to have the fine hydroxyapatite particles impregnated and absorb a drug. If the fine hydroxyapatite particles are administered into the body in this state, the absorbed drug becomes immediately released and there is no sustained drug release effect. Therefore, by filling the fine pores of the spherical-shape porous ceramics with fine hydroxyapatite particles impregnated with and absorbing the drug, it is possible to obtain a sustained release effect. (See Figs. 4(a) and 4(b).)

Example I-6

As a simulation experiment for confirming the sustained drug release effect, 10% by weight of fine hydroxyapatite particles was mixed into a 10 mM aqueous Methyl Orange solution and stirred well. This was filled into the fine pores of the spherical-shape porous ceramics by the method shown in Example I-5. 0.2 g of the sample filled in the fine pores was introduced into 200 ml of ion exchange water, then the immersion solution was taken after a predetermined time and the amount of elution of Methyl Orange was compared by the absorbance by an ultraviolet spectrophotometer. As a control, spherical-shape porous ceramics without the fine pores filled immersed in a 10 mM aqueous Methyl Orange solution was used.

As a result, it was found that the sample having the filled fine pores carried about three times the amount of Methyl Orange compared with a sample not filled. Further, as a result of the sustained release, the Methyl Orange could be released over an approximately 10 times longer period. The possibility of obtaining excellent therapeutic effects by replacing the Methyl Orange with various types of antibiotics or antitumor preparations was suggested (see Fig. 5).

Example II-1

1 g of calcium phosphate powder (#400 mesh or less) having a Ca/P = 1.48 synthesized by a known wet synthesis method was mixed into 3 g of a 10% by weight aqueous solution of polyvinyl alcohol, then 0.5 g of ion exchange water was added and the mixture further mixed and stirred. 10 ml of the slurry obtained was filled into a thermosyringe and a 24G needle (inner diameter 0.47 mm) was used to drop it into liquid nitrogen. The frozen product obtained was dried using a vacuum freeze dryer, then this was sintered at 1400°C for 5 hours to obtain 0.9 g of spherical-shape ceramics. The spherical-shape ceramics obtained had a diameter of 0.8 to 1.2 mm. (See Figs. 6(a) and 6(b).)

0.9 g of the spherical-shape ceramics obtained was inserted into a heat resistant sterile bottle, then 50 ml of ion exchange water was added and the bottle corked. This was placed in a 120°C incubator for 1 hour to make calcium phosphate crystal precipitate on the surface of the spherical-shape ceramics. This was dried in the incubator, then the surface condition was observed by a scanning-type electron microscope, whereupon it was confirmed that 10 to 20 μm calcium phosphate crystals were distributed over the entire surface. (See Fig. 7(a) and 7(b).)

Example II-2

Spherical-shape ceramics on the surface of which calcium phosphate crystal was precipitated, prepared in Example II-1, and calcium sulfate powder were mixed and then a suitable quantity of ion exchange water was added to create a cement-like state. This was kneaded for 1 minute, then the cement was filled into an eggplant-shaped flask which was then immersed in liquid nitrogen to instantaneously freeze the cement. Then, this was quickly dried using a freeze dryer. The dried sample was passed through a rated sieve #100 to remove the surplus deposited calcium sulfate to coat calcium sulfate cement on the surface and obtain a bone filler. (See Figs. 8(a) and 8(b).)

Example II-3

To investigate the state of curing of the bone filler prepared in Example II-2, a hole of a diameter of about 4 mm was bored into the rib of a hog and the bone filler was filled in the hole. After about 1 hour after filling, the bone filler completely set and it became impossible to withdraw the bone filler from the hole. This experiment confirmed the low possibility of the product of the present invention detaching from the diseased portion when filled in a portion of bone loss.

INDUSTRIAL APPLICABILITY

As explained above, according to the present

invention, it is possible to produce ceramics freely controlled in particle size and pore size simply and in a short time. Therefore, when used as a bone filler, there is the effect of promoting bone regeneration, without blocking the flow of blood in the bone. Further, by impregnating a drug in the resorbable ceramics, an ideal sustained drug release carrier is obtained.

According to the present invention, by coating a ceramic cement on the surface of ceramics with a superior biocompatibility, the cement sets by a hydrolysis reaction when implanted at the bone loss portion and anchors the ceramics sintered granules in the bone loss portion. Therefore, while past granular bone fillers had suffered from the problem of scattering from the bone loss portion, this problem has been solved by the present invention.

CLAIMS

1. A process for producing ceramics comprising dropping a starting ceramics into a low temperature medium, followed by freeze drying and then sintering the same.

2. A process for producing ceramics as claimed in claim 1, wherein the ceramics is calcium phosphate, tricalcium phosphate, calcium dihydrogenphosphate, tetracalcium phosphate, octacalcium phosphate, and a mixture of these calcium phosphates.

3. A sustained drug release product obtained by forming the ceramics obtained according to claim 1 or 2 into a porous product, followed by impregnating the pores with a drug.

4. A sustained drug release product as claimed in claim 3, wherein after the drug is impregnated into the porous ceramics, the impregnated parts are plugged by said ceramics, whereby the sustained release time of the drug is controlled.

5. A process for producing ceramics, wherein a ceramics solution is brought into contact with a low temperature medium.

6. A composite spherical ceramics having a composite layer obtained by dropping a powder of a starting material into a low temperature medium and applying a hydrothermal treatment to the spherical-shape ceramics obtained.

7. A composite spherical-shape ceramics having a composite layer as claimed in claim 6, further having a cement layer obtained by coating the surface of the composite layer with a cement.

8. A process for producing a bone filler, comprising dropping a material capable of using, as a bone filler or other biorepair material, into a low temperature medium and applying a hydrothermal treatment to the spherical-shape ceramics thus obtained under a high temperature and high pressure so as to precipitate

crystal on the surface, whereby an anchoring effect can be obtained at the time of implantation in a diseased portion.

9. A process for producing a bone filler as claimed in claim 8, wherein the surface is coated with a bone cement so as to give the anchoring effect when implanting the filler into a diseased portion.

10. A process for producing a bone filler as claimed in claim 9, wherein the coating method of the bone filler comprises instantaneously freezing a cement to be settable by crystal growth, before the crystal growth, followed by freeze drying to thereby homogeneously coat the surface of the bone filler without impairing the effect of the cement.

ABSTRACT OF THE DISCLOSURE

Spherical-shape ceramics obtained by dropping starting ceramics into a low temperature medium or composite spherical-shape ceramics having a composite layer obtained by applying a hydrothermal treatment thereto.

Fig. 1(a)

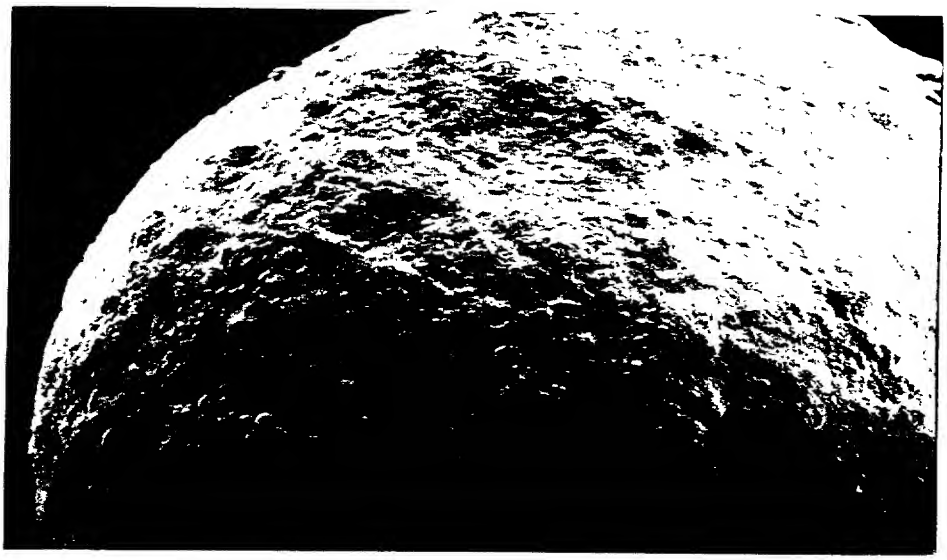

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Fig. 1(b)

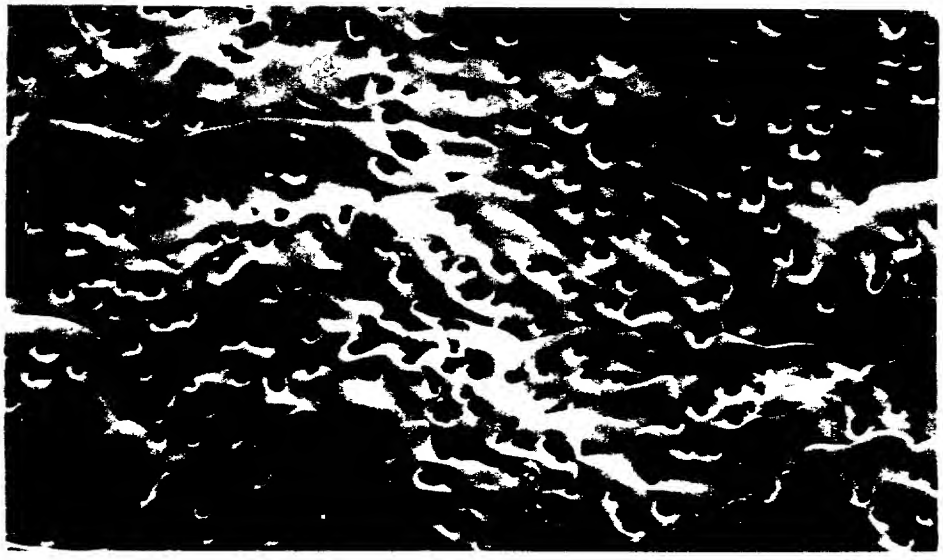

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Fig. 2(a)

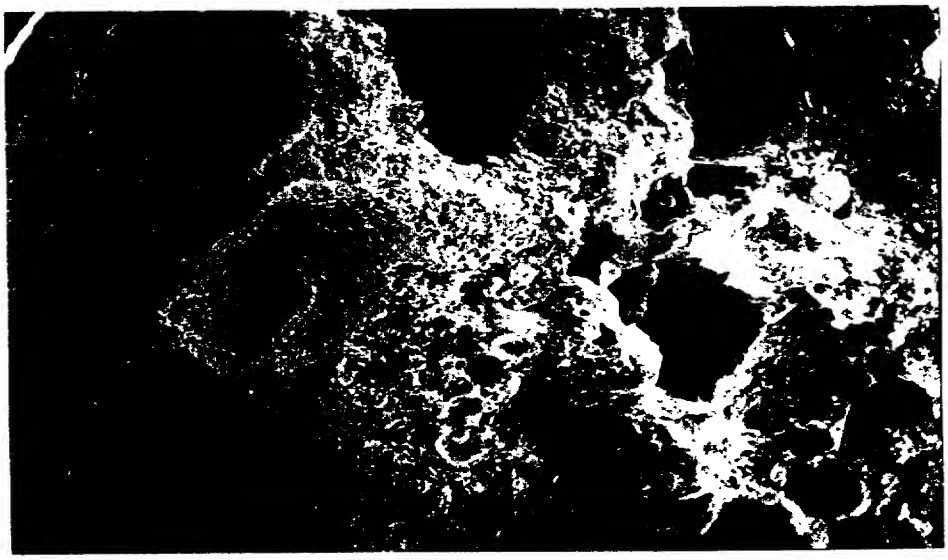

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Fig. 2(b)

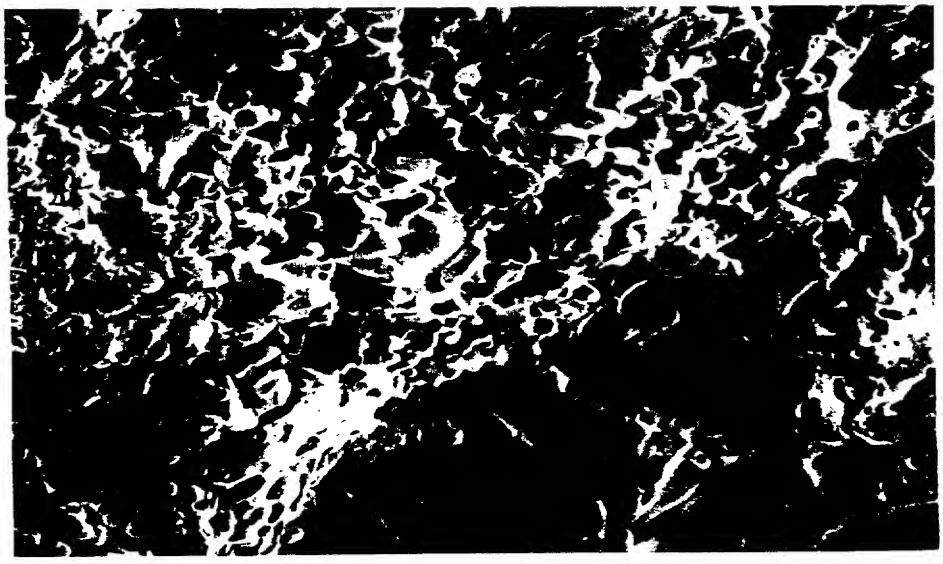

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Fig. 3(a)

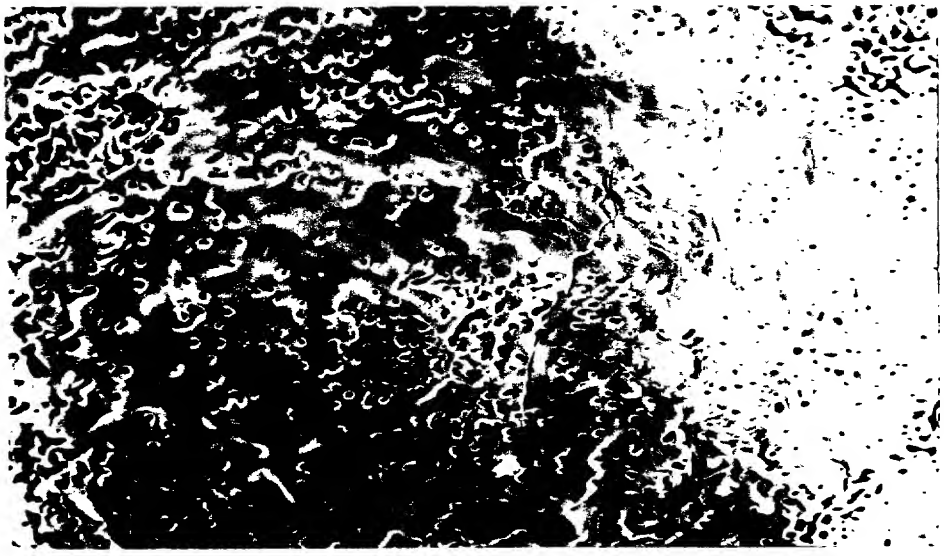

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Fig. 3(b)

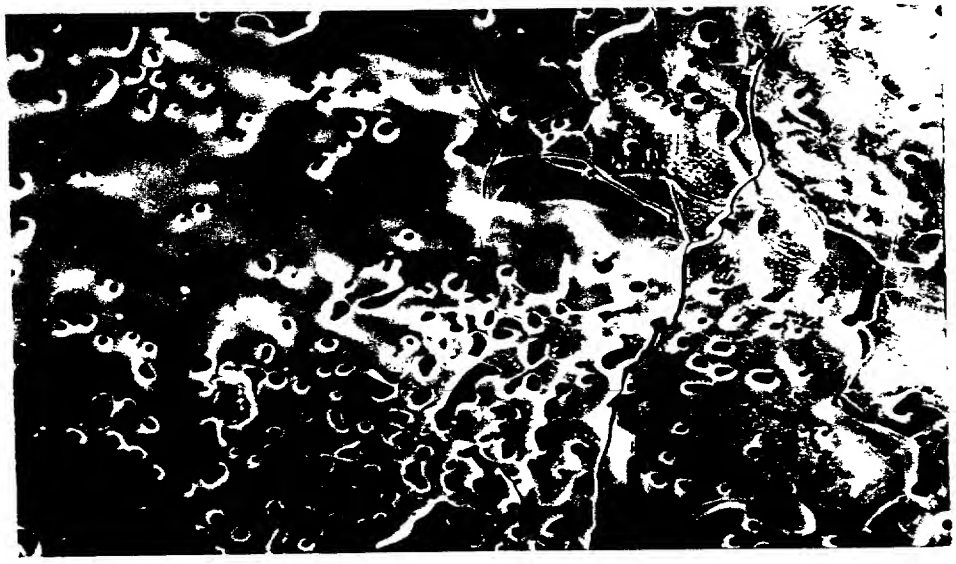

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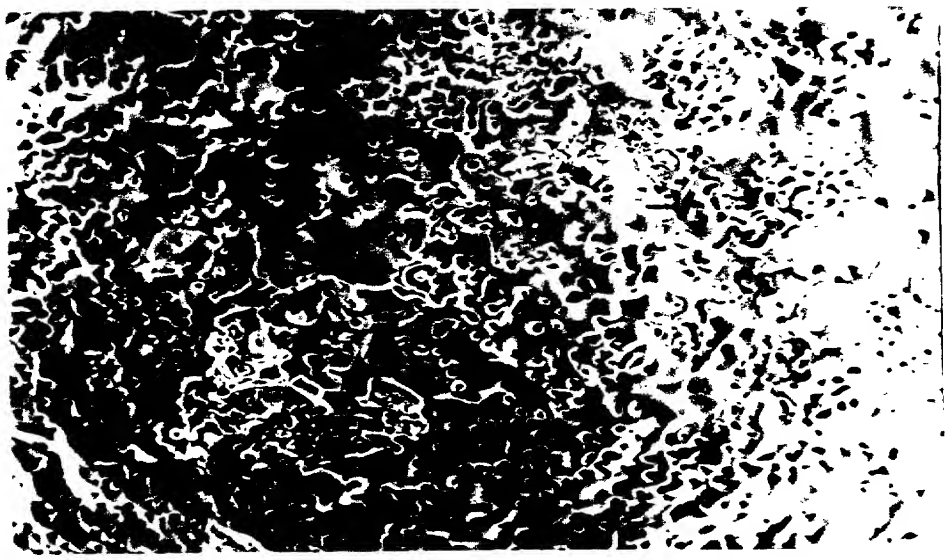
Fig.3(c)



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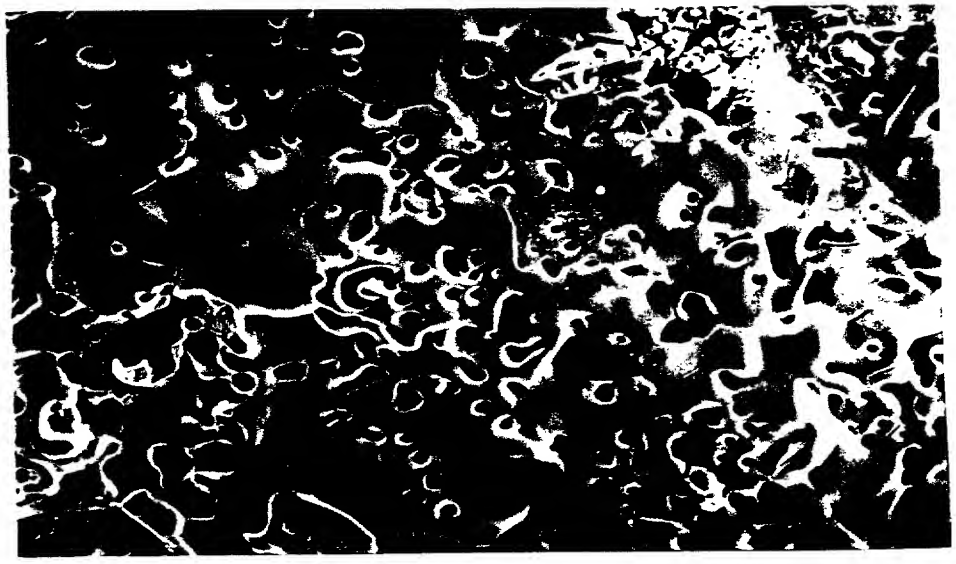

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Fig.3(e)

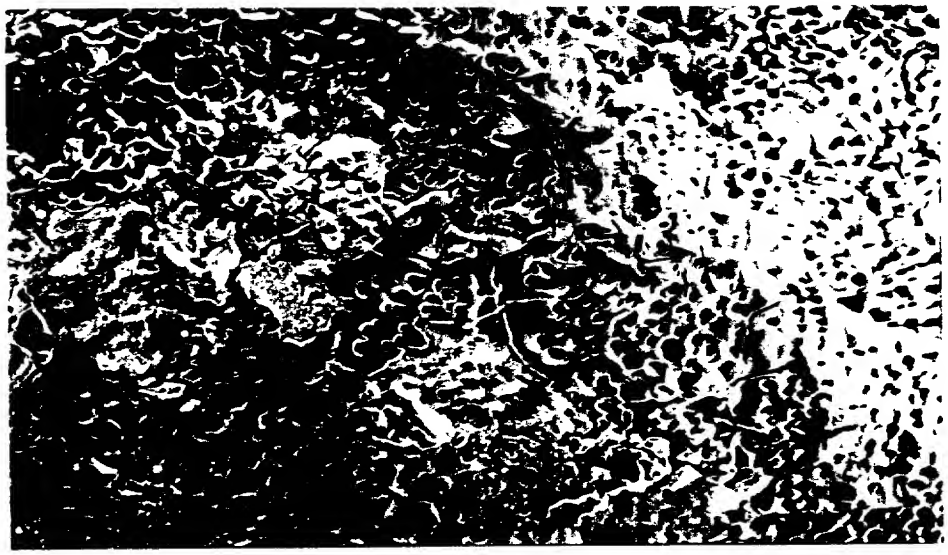

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Fig.3(f)

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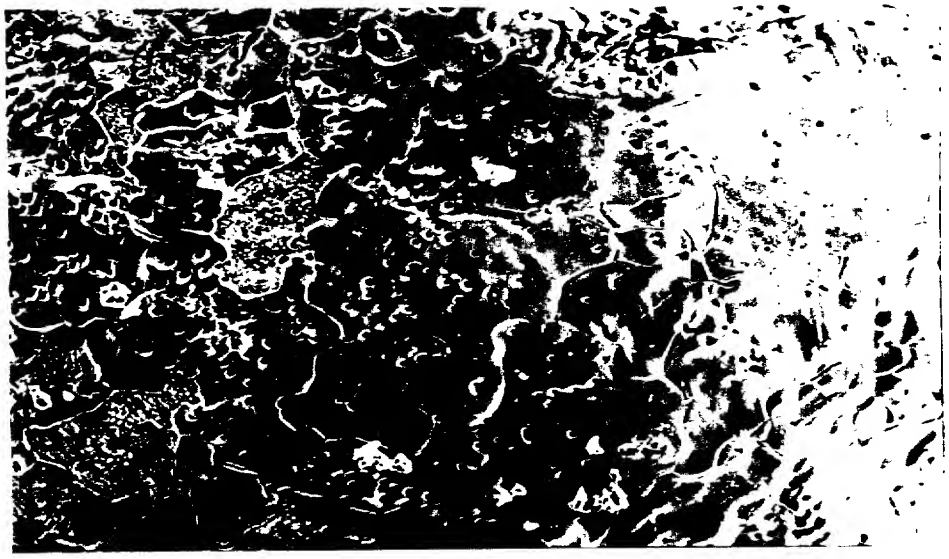
Fig. 3(g)



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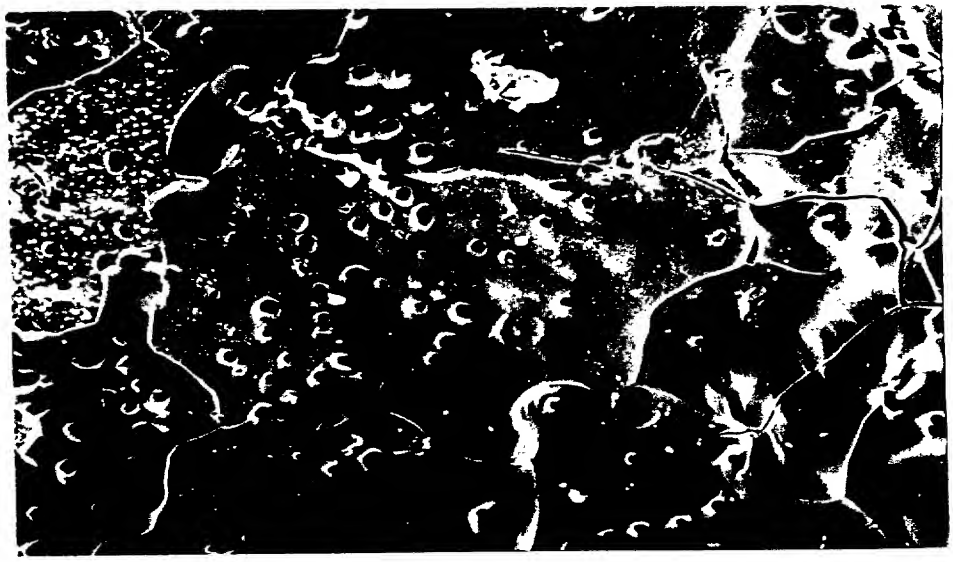

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Fig.3(i)

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Fig.3(j)

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Fig.4(a)

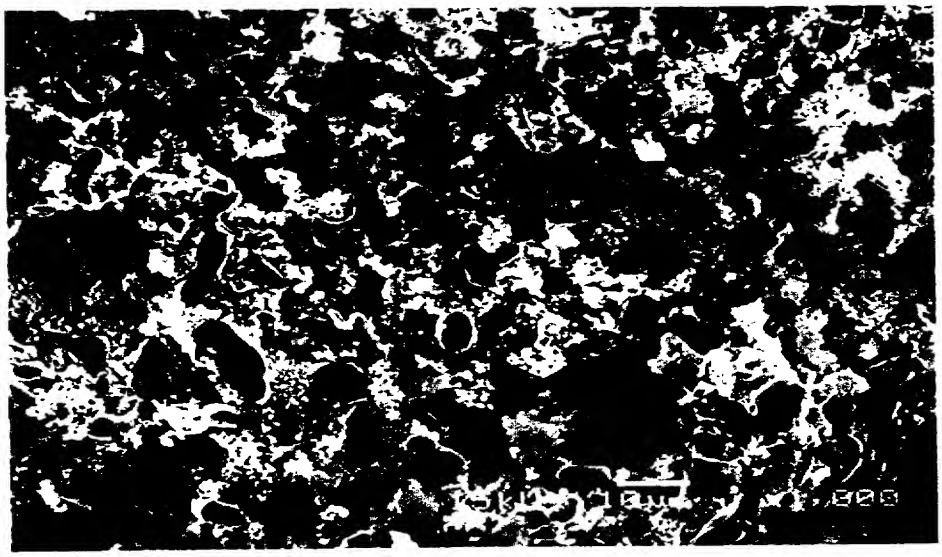

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Fig.4(b)

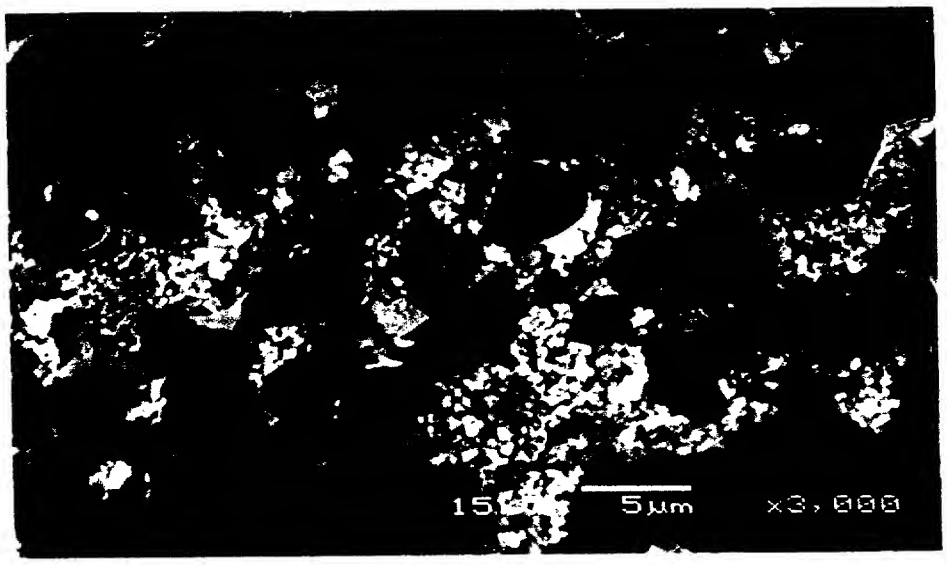

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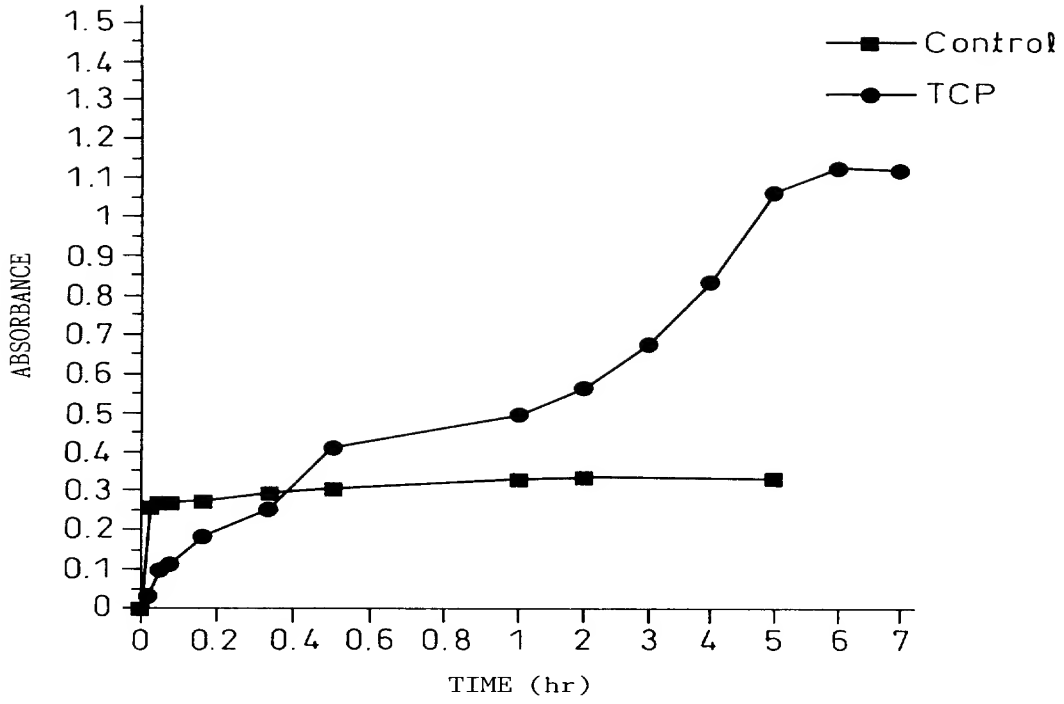
Fig. 5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1.4
1.3
1.2
1.1
1
0.9
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0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
2
3
4
5
6
7
TIME (hr)

Fig.6(a)

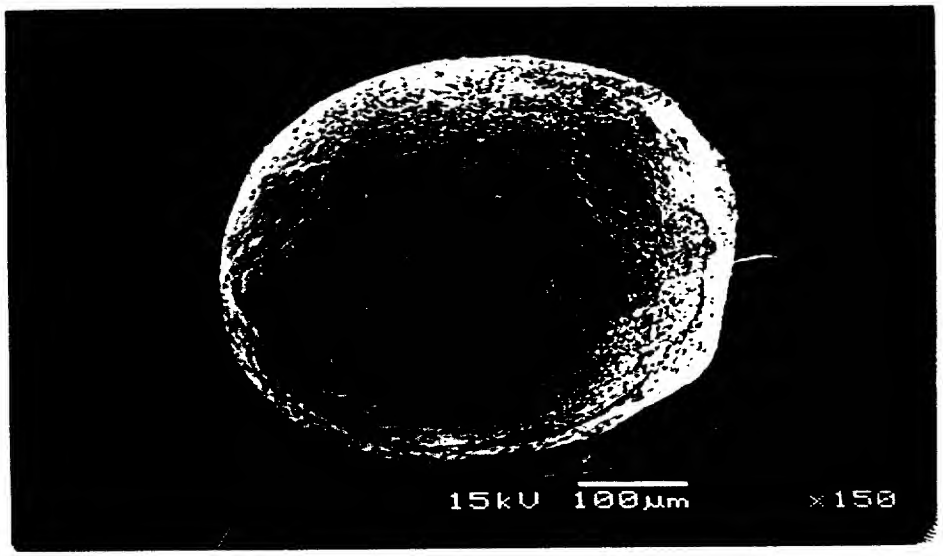

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Fig.6(b)

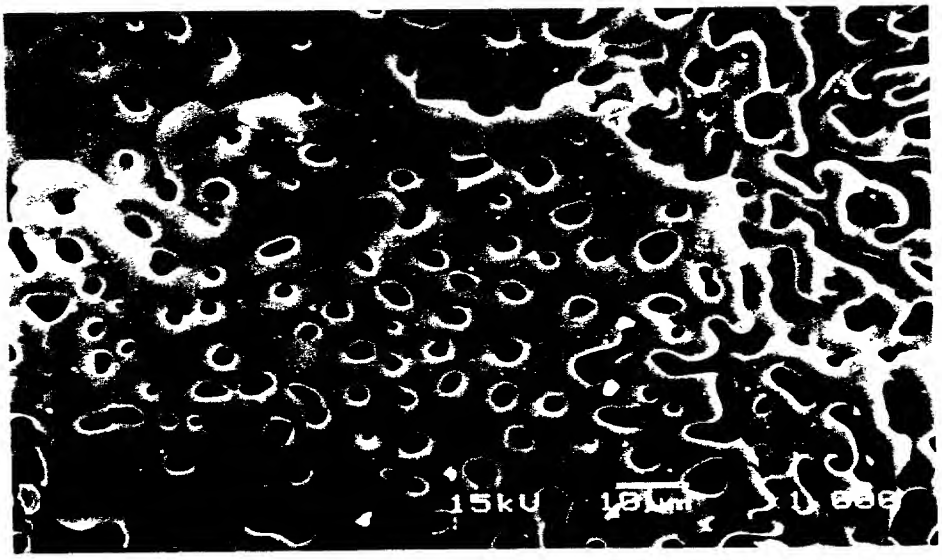

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Fig. 7(a)

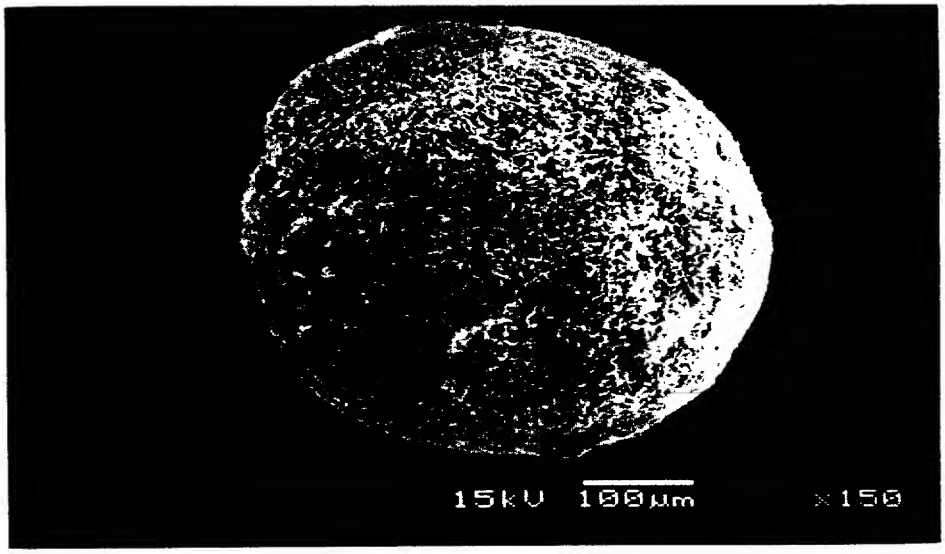

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Fig. 7(b)

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Fig. 8(a)

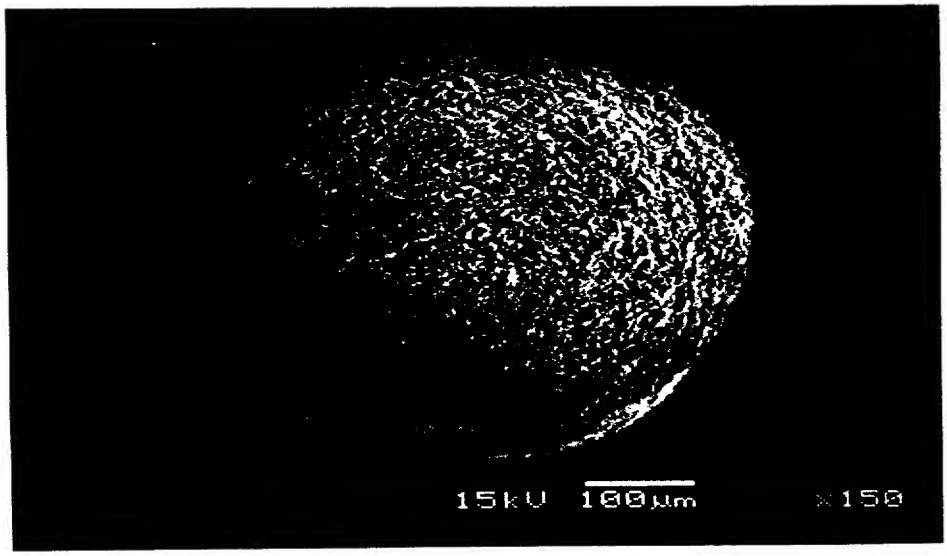

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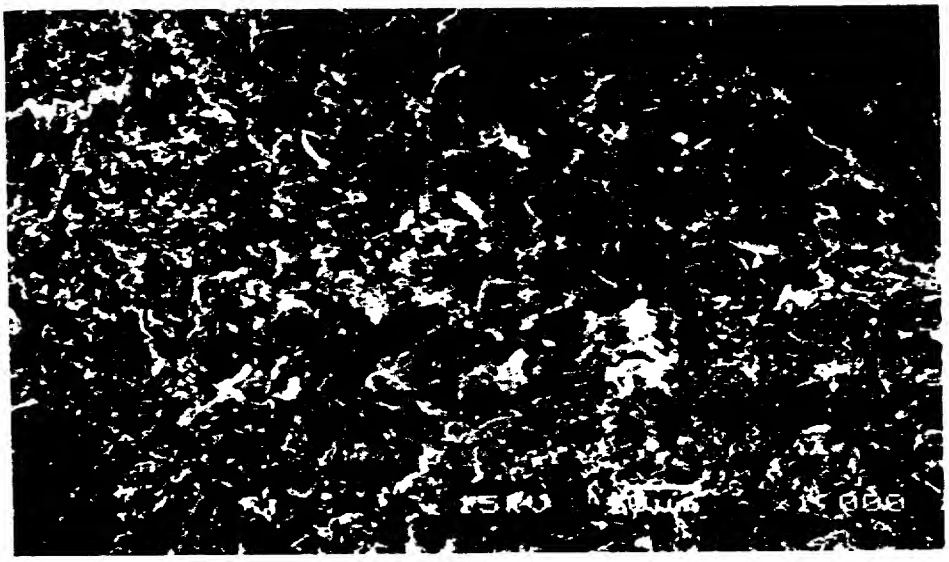
Fig. 8(b)



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Docket No. 34650/DBP/A400

(Christie)

PTO/SB/106 (8-96)
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As a below named inventor, I hereby declare that:

私の住所、私書箱、国籍は下記の私の氏名の後に記載された通りです。

My residence, post office address and citizenship are as stated next to my name.

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I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PROCESS FOR PRODUCING CERAMICS

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（該当する場合）_____に訂正されました。

☒ was filed on November 25, 1997
as United States Application Number or
PCT International Application Number
PCT/JP97/04288 and was amended on
_____ (if applicable).

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

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I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

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I hereby claim foreign priority under Title 35, United States Code, Section 119 (a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)
外国での先行出願

(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	Priority Not Claimed 優先権主張なし
8-328012(Pat. Appln.)	Japan	25/November/1996	☐
9-201033(Pat. Appln.)	Japan	11/July/1997	☐

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I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

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(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況：特許許可済、係属中、放棄済)

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委任状： 私は下記の発明者として、本出願に関する一切の手続きを米特許商標局に対して遂行する弁理士または代理人として、下記の者を指名いたします。（弁護士、または代理人の氏名及び登録番号を明記のこと）

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith *(list name and registration number)*

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第二共同発明者	Full name of second joint inventor, if any Takehiko Arai
第二共同発明者 日付	Second inventor's signature Takehiko Arai. Date May 17, 1999
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（第三以降の共同発明者についても同様に記載し、署名をすること）

(Supply similar information and signature for third and subsequent joint inventors.)

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